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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,047	10/20/2005	Tadao Saito	SPO-120	9241

23557 7590 12/30/2008

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
12/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,047	SAITO ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted October 15, 2008 wherein claims 7, 11, ands 17 are amended, claim 12 is cancelled, and new claims 19-22 are cancelled. This application is a national stage application of PCT/JP03/09324, filed July 23, 2003, which claims priority to foreign applications JP2002-213305, filed July 23, 2002, and JP2003-50739, filed February 27, 2003.

Claims 7-11 and 15-22 are pending in this application.

Claims 7-11 and 15-22 as amended are examined on the merits herein.

The declaration of Haruki Kitazawa, submitted October 15, 2008, under 37 CFR 1.132, has been fully considered and entered into the record. The declaration is discussed further below as it relates to the rejections of record in the previous office action.

Applicant's amendment, submitted October 15, 2008, with respect to the rejection of instant claims 7-9, 17, and 18 under 35 USC 102(e) for being anticipated by King, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require that the dextran have a molecular weight of at least 100000 Da. Therefore the rejection is withdrawn.

Applicant's amendment, submitted October 15, 2008, with respect to the rejection of instant claim 11 under 35 USC 102(b) for being anticipated by Suzuki et al.,

has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require that the dextran have a molecular weight of at least 100000 Da. Therefore the rejection is withdrawn.

Applicant's amendment, submitted October 15, 2008, with respect to the rejection of instant claims 11 and 12 under 35 USC 102(e) for being anticipated by JP52028583, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require that the dextran have a molecular weight of at least 100000 Da. Therefore the rejection is withdrawn.

Applicant's amendment, submitted October 15, 2008, with respect to the rejection of instant claims 7-11, 15, and 16 under 35 USC 102(b) for being anticipated by Suzuki et al. W, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require that the dextran have a molecular weight of at least 100000 Da. Therefore the rejection is withdrawn.

Applicant's amendment, submitted October 15, 2008, with respect to the rejection of instant claims 11 and 12 under 35 USC 103(a) for being obvious over Suzuki et al. R4 in view of Sacco et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to require that the dextran have a molecular weight of at least 100000 Da. Therefore the rejection is withdrawn.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a specific disease, does not reasonably provide enablement for a method of preventing a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of a disorder. In the absence of an explicit definition in

Applicant's specification, the claims are given their broadest reasonable interpretation. See MPEP 2111. Merriam-Webster's Collegiate Dictionary (Of record in previous action) defines "prevent" as meaning, "to deprive of power or hope of acting or succeeding," or "to keep from happening or existing." This definition is taken as representing the ordinary usage of the term "preventative". In order to deprive something of power or hope of acting or succeeding, the preventative agent must be completely effective. "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The state of the prior art: Various dietary polysaccharides, including negatively charged and phosphorylated polysaccharides, are known in the art to exert certain biological effects, including being useful for treating disease. They are not, however, known to be useful for preventing any disease in the sense described above under the heading Nature of the Invention.

In general, preventing infectious disease or allergies, according to the definition of prevention given below under the heading "breadth of the claims" is not possible as these conditions are linked to exposure to an external pathogenic agent or allergen which triggers the disease. No chemical or other active agent can control a subject's surrounding to prevent exposure to a sufficiently strong allergen or infectious agent. Also, both infectious agents and allergens are extremely diverse and no singe compound can be expected to perfectly block the actions of each and every one. More

generally, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the

subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at preventing a disorder.

The amount of direction or guidance presented: No guidance is given in the specification suggesting any reason to believe that administration of a phosphorylated dextran can achieve complete prevention of infectious disease, allergy, or any other condition.

The presence or absence of working examples: No working examples are given.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the nature of the invention and the unpredictability of the art, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of any disorder including those recited in instant claims 17 and 18.

Response to Argument: Applicant's arguments, submitted October 15, 2008, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the term "preventing" used in the claims should be interpreted according to its commonly used meaning as understood in the art. However, claims are interpreted according to the **broadest reasonable interpretation**, not the customary interpretation as alleged by Applicant. In the instant circumstances, the broadest reasonable interpretation of "prevention" is the one given above, which includes methods that are capable of absolutely blocking all effects of a condition.

With respect to the declaration of Haruki Kitazawa, the results presented in the declaration deal with the induction of immune response in mice and its suppression by co-administration of phosphorylated dextran. This is not a preventative method as it requires that the phosphorylated dextran be administered **at the same time as** the antigenic stimulus.

For these reasons the rejection is deemed proper and maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-10, 15-19, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bijlsma et al. (US patent 6686341, cited in PTO-892, also published as WO00/57727, also included with PTO-892).

Bijlsma et al. discloses compositions containing negatively charged non-digestible polysaccharides having a molecular weight of 8-4000 kD. (column 1 lines 47-52) These polysaccharides contain negatively charged groups such as phosphate, with preferably one charged group per 10-10000 saccharide units. (column 2 lines 55-62) Polysaccharides that can be modified in this manner include dextrans. (column 2 line 66 – column 3 line 15) These compositions can be administered to a subject to prevent the entrance of toxic or allergenic substances through the tight junctions of the intestinal wall. (column 4 lines 9-21) The negatively charged polysaccharides are administered as foods or supplements, which are seen to include ingredients considered to be pharmaceutical carriers. (column 4 lines 28-35) These compositions can be used to treat allergies and allergic reactions in the intestines. (column 4 lines 36-42) Several compositions containing these polysaccharides are disclosed in columns 6-7. Example

4 in column 5 lines 60-67 discloses a method for phosphorylating guar by dissolving it in phosphate buffer, heating and drying it, and then heading the dried material at 140C for 2 hours. Bijlsma et al. does not teach the specific active ingredient phosphorylated dextran having a molecular weight of at least 100000 in a composition in which at least 90% of the dextran polysaccharides are phosphorylated.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Bijlsma et al. with phosphorylated dextran. One of ordinary skill in the art would have been motivated to do so because Bijlsma et al. already discloses phosphate as one of the negatively charged groups that can be used in this method with dextrans. One of ordinary skill in the art would reasonably have expected success because making the specific embodiments of a generic prior art teaching is well within the ordinary and routine level of skill in the art.

As regards the molecular weight limitation of over 100 kD, Bijlsma et al. discloses polysaccharides from 8-40000 kD, a broad range substantially overlapping the claimed range. One of ordinary skill in the art would have reasonably been able to make and use specific embodiments of the claimed invention, for example those dextrans having a molecular weight of over 100 kD. Furthermore as regards the limitation that at least 90% of the dextran molecules be phosphorylated, the polysaccharides disclosed by Bijlsma et al. can have as many as 1 in 10 or 1 in 3 saccharide units modified with a phosphate group. Since polysaccharides of over 10 kD will have mare than about 500 saccharide units per polymer, each polysaccharide will bear multiple phosphate groups, and substantially all of them will have at least one phosphate group, thereby meeting

the requirements of this limitation that at least 90% of the molecules of dextran be phosphorylated.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted October 15, 2008, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the polysaccharides of Bijlsma et al. are only slightly negatively charged and do not have at least 90% of the total dextran molecules phosphorylated. However, the limitation as it currently reads requires only that at least 90% of the polymers in the sample are phosphorylated (have at least one saccharide unit bearing a phosphate). As discussed in the body of the rejection, the slightly negatively charged polymers of Bijlsma et al. do in fact have at least one phosphate per polymer, thereby meeting this limitation. Note that the limitation is not written in such as way as to require that at least **90% of the saccharide units** in each polymer be phosphorylated, which appears to be Applicant's intent in introducing the limitation.

For these reasons the rejection is deemed proper and maintained.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bijlsma et al. as applied to claims 7-10, 15-19, and 21 above, and further in view of Tarelli et al. (Reference included with PTO 1449 submitted October 26, 2005)

The disclosure of Bijlsma et al. is discussed above. Bijlsma et al. does not disclose a method whereby a dextran is reacted under heat with a phosphate buffer, freeze-dried, and heated for 24 hours according to instant claim 22.

Tarelli et al. discloses a method of phosphorylating saccharides and other OH-containing compounds wherein the polysaccharide is dissolved in a phosphate buffer, freeze-dried, and heated to 56C for a period of days. (p. 197, left column fourth paragraph, p. 19 table 1)

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a phosphorylated dextran for use in the invention of Bijlsma et al., using the freeze-drying and 24 hour heating steps as described by Tarelli et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Bijlsma et al. already discloses phosphorylating a polysaccharide by drying it in a phosphate buffer and heating it, and Tarelli et al. additionally teaches using freeze-drying in the drying step and heating the dried sample for longer periods of time. One of ordinary skill in the art would reasonably have expected success because both references are directed toward the same end (phosphorylating hydroxyl compounds) and because freeze drying and drying under heat are recognized as accomplishing the same function of drying a sample. With regard to specific temperatures and incubation

times, one of ordinary skill in the art would have been able to determine the optimal temperature, incubation time, and other such parameters to use in the method of the invention.

Therefore the invention take as a whole is *prima facie* obvious.

Claims 11 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bijlsma et al. as applied to claims 7-10, 15-19, and 21 above, and further in view of Suzuki et al. R4 (Reference of record in previous action) in view of Sacco et al. (Reference of record in previous action)

The disclosure of Bijlsma et al. is discussed above. Bijlsma et al. does not disclose a method whereby a dextran is reacted under heat with a phosphate buffer, freeze-dried, and heated for 24 hours according to instant claim 22.

Suzuki et al. R4 discloses a phosphorylated dextran and a method of making said dextran phosphate by reacting the dextran with polyphosphoric acid and triethylamine in anhydrous formamide. (p. 228, third paragraph) Suzuki et al. R4 does not teach a heating step in the reaction.

Sacco et al. discloses a method of phosphorylating dextran comprising heating dextran in the presence of tributylamine and polyphosphoric acid. (p. 194, third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to make the dextran phosphates of Bijlsma et al. by the reaction of Suzuki et al. R4 carried out under heating. One of ordinary skill in the art would have been

motivated to use this method for producing the products used in the method of Bijlsma et al. because it is disclosed to be useful for adding phosphate groups to dextran, thereby producing a negatively charged polymer. One of ordinary skill in the art would have recognized that Sacco et al. suggests adding heat to the phosphorylation reaction to speed up the rate of the reaction, since Sacco et al. describes a similar reaction, using a similar base and solvent, being carried out under heating.

Thus the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
12/22/2008

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623